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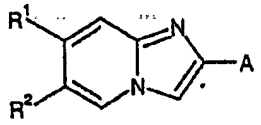
(54) Title: IMIDAZO (1,2-A)-PYRIDINE DERIVATIVES AS MGLUR5 ANTAGONISTS

(57) Abstract: This invention relates to the use of compounds of the general formula wherein R^1 and R^2 signify hydrogen, (C_{1-6})-alkyl, halogen, hydroxy, (C_{1-6})-alkoxy and A has the significance given in the description, as well as pharmaceutically acceptable salts thereof, for the manufacture of medicaments for the treatment or prevention of GluR5 receptor mediated disorders, such as acute and/or chronic neurological disorders.

IMIDAZO (1,2-A)-PYRIDINE DERIVATIVES AS MGLUR5 ANTAGONISTS

The present invention relates to the use of imidazo[1,2-a]pyridine derivatives of the general formula



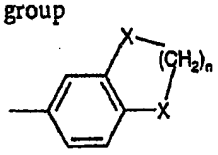
I

wherein

R^1 signifies hydrogen, (C_{1-6})-alkyl, halogen, hydroxy, or (C_{1-6})-alkoxy;

R^2 signifies hydrogen, (C_{1-6})-alkyl, halogen, hydroxy, or (C_{1-6})-alkoxy; and

A signifies unsubstituted aryl or aryl substituted with one or more substituents selected from the group consisting of (C_{1-6})-alkyl, halogen, halogen-(C_{1-6})-alkyl, hydroxy, (C_{1-6})-alkoxy, benzyloxy, amino, (C_{1-6})-alkylamino, di-(C_{1-6})-alkyl-amino, arylamino, diarylamino or nitro, or signifies unsubstituted heteroaryl or heteroaryl substituted with one or more substituents selected from the group consisting of (C_{1-6})-alkyl, halogen, halogen-(C_{1-6})-alkyl, hydroxy, (C_{1-6})-alkoxy, benzyloxy, amino, (C_{1-6})-alkylamino, di-(C_{1-6})-alkyl-amino, arylamino, diarylamino or nitro or signifies the group



wherein
X is, independently from each other, $-CH_2-$ or -O-; and
n is 1 or 2;

and their pharmaceutically acceptable salts for the manufacture of medicaments for the treatment or prevention of mGluR5 receptor mediated disorders.

Some compounds of the present formula I are known compounds and have been described in the literature. The synthesis of some imidazo[1,2-a]pyridine derivatives has

for example been described in *Recl. Trav. Chim. Pays-Bas* 1949, 68, 441-470, in *J. Org. Chem.* 1954, 19, 1370-1374, in *J. Heterocyclic Chem.* 1988, 25, 129-137, in International patent application WO 00/08021 or in *J. Org. Chem.* 2000, 65, 9201-9205. According to *J. Prakt. Chem* 1971, 313, 977-985, imidazo[1,2,-a]pyridines bearing a benzothienyl, thienyl or benzofuranyl group have been prepared by condensation of α-haloketones or α-hydroxyketones with amidines. The synthesis and antimicrobial action of furyl derivatives of imidazo[1,2-a]pyrimidine has been reported in *Khim.-Farm. Zh.* 1970, 4, 20-26.

Different uses have been described for imidazo[1,2-a]pyridine derivatives. The preparation of 2-[p-(dimethylamino)phenyl]-imidazo[1,2-a]pyridine as an azo dye and its evaluation as disperse dye on synthetic fibers, cellulose acetate, and cotton has been described in *Boll. Sci. Fac. Chim. Ind. Bologna* 1966, 24, 205-214. Fluorescent properties of imidazo[1,2-a]-pyridine-based compounds have been described in *Bull. Chem. Soc. Jpn.* 1999, 72(6), 1327-1334. In Japanese patent applications JP 50-140477, JP 51-004194 and JP 51-125095 have been reported the analgesic, antiinflammatory, antipyretic, and local anesthetic activities of certain phenyl-imidazo[1,2-a]pyridines wherein the phenyl ring is substituted by $-CR^1R^2COOH$, $-CR^1R^2COOR$, $-CR^1R^2CONH_2$, $-CR^1R^2CSNH_2$, $-CR^1R^2CN$, $-CO_2-(CH_2)_{1-4}-NR^3R^4$ or $-CH_2OH$ and R, R^1, R^2, R^3 and R^4 are hydrogen or alkyl. According to *Arzneim.-Forsch.* 1981, 31(7), 1111-1118, the most preferred compound thereof, viz. 4-imidazo[1,2-a]pyridin-2-yl-α-methyl-benzeneacetic acid (miroprofen) has been effective in suppressing pain responses and acute inflammation accompanied by increased vascular permeability. The use of imidazo[1,2-a]pyridines which are substituted at the 2 and 6 positions as anthelmintic and fungicidal agents has been disclosed in US patent No. 3,701,780. Isothiocyanato derivatives like 2-(4-isothiocyanato-phenyl)-6-methyl-imidazo[1,2-a]pyridine have been described as antihelmintics in Swiss patent No. CH 590 862.

The use of imidazo[1,2-a]pyridine derivatives as inhibitors for STAT6 6 transcription factor activation and IL 4 antagonists for treatment of allergic, autoimmune, parasital, viral, and bacterial diseases, tumors, host-vs. graft syndrome, systemic lupus erythematosus, and AIDS has been disclosed in Japanese patent application No. JP 11-116481.

According to *Eur. J. Med. Chem.* 1994, 29(5), 339-342, aryl- or pyridyl-substituted fused imidazoles like for example 2-(4-pyridinyl)-imidazo[1,2-a]pyridine possess cardiotonic activity. N-(4-imidazo[1,2-a]pyridin-2-yl-phenyl)-methanesulfonamide has been prepared as antithrombotic and cardiovascular agent in European patent application EP 0 185 345. According to *Eur. J. Med. Chem.* 1987, 22(5), 457-462, certain imidazo[1,2-a]pyrimidines, e.g. 2-(2-furanyl)-imidazo[1,2-a]pyridine, have been tested for bronchodilator activity and for inhibition of a cardiac phosphodiesterase. Phosphonic acid

derivatives of imidazo[1,2-a]pyridines, e.g. [5-(6-chloroimidazo[1,2-a]pyridin-2-yl)-2-furanyl]-phosphonic acid, have been described as human liver fructose-1,6-bisphosphatase inhibitors in International patent application WO 98/39342.

N,N,6-trimethyl-2-(4-methylphenyl)-imidazo[1,2-a]pyridine-3-acetamide (Zolpidem) and its use as anticonvulsant and hypnotic has been firstly disclosed in European patent application EP 0 050 563. Further imidazo[1,2-a]pyridine derivatives with anticonvulsant, hypnotic and anxiolytic activity have been also described in the patent applications EP 0 092 458, EP 0 092 459, EP 0 172 096, FR 25 81 646, EP 0 234 970, EP 0 251 859 and EP 0 267 111. It has been shown in *Eur. J. Pharmacol.* 1986, 130(3), 257-263, that Zolpidem possesses agonist properties at central benzodiazepine receptors and according to *Br. J. Pharmacol.* 2000, 131(7), 1251-1254 the mechanism of action in vivo is based on its high affinity to the α1-GABAA receptor benzodiazepine site.

It has now surprisingly been found that the compounds of general formula I are metabotropic glutamate receptor antagonists. Compounds of formula I are distinguished by having valuable therapeutic properties. They can be used in the treatment or prevention of mGluR5 receptor mediated disorders.

In the central nervous system (CNS) the transmission of stimuli takes place by the interaction of a neurotransmitter, which is sent out by a neuron, with a neuroreceptor.

Glutamate is the major excitatory neurotransmitter in the brain and plays a unique role in a variety of central nervous system (CNS) functions. The glutamate-dependent stimulus receptors are divided into two main groups. The first main group, namely the ionotropic receptors, forms ligand-controlled ion channels. The metabotropic glutamate receptors (mGluR) belong to the second main group and, furthermore, belong to the family of G-protein coupled receptors.

At present, eight different members of these mGluR receptors are known and some of these even have sub-types. According to their sequence homology, signal transduction mechanisms and agonist selectivity, these eight receptors can be sub-divided into three sub-groups:

mGluR1 and mGluR5 belong to group I, mGluR2 and mGluR3 belong to group II and mGluR4, mGluR6, mGluR7 and mGluR8 belong to group III.

Ligands of metabotropic glutamate receptors belonging to the first group can be used for the treatment or prevention of acute and/or chronic neurological disorders such as psychosis, epilepsy, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits, as well as chronic and acute pain.

Other treatable indications in this connection are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are ischemia, Huntington's chorea, amyotrophic lateral sclerosis (ALS), dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficiency functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, opiate addiction, anxiety, vomiting, dyskinesia and depressions.

Disorders mediated full or in part by mGluR5 are for example acute, traumatic and chronic degenerative processes of the nervous system, such as Alzheimer's disease, senile dementia, Parkinson's disease, Huntington's chorea, amyotrophic lateral sclerosis and multiple sclerosis, psychiatric diseases such as schizophrenia and anxiety, depression and pain. Selective mGluR5 antagonists are especially useful for the treatment of anxiety and pain.

Objects of the present invention are the use of compounds of formula I and their pharmaceutically acceptable salts for the manufacture of medicaments for the treatment or prevention of mGluR5 receptor mediated disorders, such as acute and/or chronic neurological disorders, cognitive disorders and memory deficits such as Alzheimer's disease, senile dementia, Parkinson's disease, ischemia, Huntington's chorea, amyotrophic lateral sclerosis and multiple sclerosis, psychiatric diseases such as psychosis, epilepsy, schizophrenia, anxiety and depression as well as chronic and acute pain.

The following definitions of general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination. The term "(C_{1-6})-alkyl" used in the present description denotes straight-chain or branched saturated hydrocarbon residues with 1 to 6 carbon atoms, preferably with 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl and the like.

The term "halogen" denotes fluorine, chlorine, bromine and iodine.

The term "halogen-(C_{1-6})-alkyl" denotes (C_{1-6})-alkyl, wherein the hydrogen atoms are replaced by one or more halogen atoms.

The term "(C_{1-6})-alkoxy" denotes a (C_{1-6})-alkyl group as defined hereinbefore, which is bound via an oxygene atom, e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and the like.

"Aryl" represents an aromatic carbocyclic group consisting of one individual ring, or one or more fused rings in which at least one ring is aromatic in nature. Preferred aryl groups are phenyl or naphthyl.

The term "heteroaryl" refers to an aromatic 5- or 6-membered ring containing one or more heteroatoms selected from nitrogen, oxygen or sulphur, or to a bicyclic aromatic group comprising two 5- or 6-membered rings, in which one or both rings can contain one or more heteroatoms selected from nitrogen, oxygen or sulphur. Examples of such heteroaryl goups are furyl, pyrrolyl, thienyl (thiophenyl), 1H-imidazolyl, 2H-imidazolyl, 4H-imidazolyl, 1H-pyrazolyl, 3H-pyrazolyl, 4H-pyrazolyl, 1,2-oxazolyl, 1,3-oxazolyl, [1,2,4]triazolyl, [1,2,3]triazolyl, [1,2,4]oxadiazolyl, [1,3,4]oxadiazolyl, [1,2,3]oxadiazolyl, tetrazolyl, [1,2,3,4]oxatriazolyl, [1,2,3,5]oxatriazolyl, 1,3-thiazolyl, 1,2-thiazolyl, pentazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, benzofuryl (benzofuranyl), benzothienyl (benzothiophenyl), benzimidazolyl, benzo[1,4]dioxinyl, benzoxazolyl, benzothiazolyl, indolyl, isoindolyl, quinolyl, isoquinolyl and their dihydro derivatives.

Preferred heteroaryl groups are thienyl, benzofuryl or benzothienyl.

The term"(C_{1-6})-alkylamino" denotes a straight-chain or branched alkyl chain having from one to six carbon atoms attached to an amino group. Examples of such (C_{1-6})-alkylamino groups are methylamino, ethylamino, isopropylamino and the like.

"Di-(C_{1-6})-alkylamino" represents two straight-chain or branched dialkyl chains having from one to six carbon atoms attached to an amino group. Examples of such di-(C_{1-6})-alkylamino groups are dimethylamino, ethylmethylamino and the like.

"Arylamino" denotes an aryl group as defined above attached to an amino group. A phenylamino group is an example of such a group.

The term "pharmaceutically acceptable salt" refers to any salt derived from an inorganic or organic acid or base.

Preferred compounds of formula I for the above mentioned use are those, in which A signifies unsubstituted aryl or aryl substituted with one or more substituents selected from the group consisting of (C_{1-6})-alkyl, halogen, halogen-(C_{1-6})-alkyl, hydroxy, (C_{1-6})-alkoxy, benzyloxy, amino, (C_{1-6})-alkylamino, di-(C_{1-6})-alkyl-amino, arylamino, diarylamino or nitro.

Especially preferred for the above mentioned use are those compounds of formula I, in which A signifies unsubstituted phenyl or phenyl substituted with one or more substituents selected from the group consisting of (C_{1-6})-alkyl, halogen, halogen-(C_{1-6})-

alkyl, hydroxy, (C_{1-6})-alkoxy, benzyloxy, amino, (C_{1-6})-alkylamino, di-(C_{1-6})-alkylamino, arylamino, diarylamino or nitro.

Even more preferred for the above mentioned use are compounds of formula I, in which A signifies phenyl substituted with one substituent selected from the group consisting of (C_{1-6})-alkyl, halogen, halogen-(C_{1-6})-alkyl, hydroxy, (C_{1-6})-alkoxy, benzyloxy, amino, (C_{1-6})-alkylamino, di-(C_{1-6})-alkyl-amino, arylamino, diarylamino or nitro.

The following are examples of such compounds:
2-(3-bromo-phenyl)-imidazo[1,2-a]pyridine,
2-(3-iodo-phenyl)-imidazo[1,2-a]pyridine,
2-(3-chloro-phenyl)-imidazo[1,2-a]pyridine,
2-(3-methyl-phenyl)-imidazo[1,2-a]pyridine,
2-(3-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine,
2-(3-fluoro-phenyl)-imidazo[1,2-a]pyridine,
7-methyl-2-phenyl-imidazo[1,2-a]pyridine,
2-(4-methyl-phenyl)-imidazo[1,2-a]pyridine,
2-(3-methoxy-phenyl)-imidazo[1,2-a]pyridine,
6-methyl-2-(4-methyl-phenyl)-imidazo[1,2-a]pyridine, or
2-(3-nitro-phenyl)-imidazo[1,2-a]pyridine.

Further preferred are those compounds of formula I for the above mentioned use, in which A signifies phenyl substituted with at least two substituents selected from the group consisting of (C_{1-6})-alkyl, halogen, halogen-(C_{1-6})-alkyl, hydroxy, (C_{1-6})-alkoxy, benzyloxy, amino, (C_{1-6})-alkylamino, di-(C_{1-6})-alkylamino, arylamino, diarylamino or nitro.

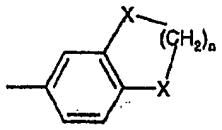
Examples for such compounds are
7-chloro-2-(3,4-dimethyl-phenyl)-imidazo[1,2-a]pyridine,
2-(3,4-dimethoxy-phenyl)-7-methyl-imidazo[1,2-a]pyridine,
2-(3,4-dimethoxy-phenyl)-imidazo[1,2-a]pyridine,
2-(3,4-dimethyl-phenyl)-7-methoxy-imidazo[1,2-a]pyridine,
2-(3,4-dimethoxy-phenyl)-7-methoxy-imidazo[1,2-a]pyridine,
2-(3,4-dimethyl-phenyl)-imidazo[1,2-a]pyridine hydrochloride,
2-(3,4-dimethyl-phenyl)-7-methyl-imidazo[1,2-a]pyridine,
2-(3-bromo-4-fluoro-phenyl)-imidazo[1,2-a]pyridine,
2-(4-benzyloxy-3-methoxy-phenyl)-imidazo[1,2-a]pyridine,
2-(3,4-dimethyl-phenyl)-7-ethyl-imidazo[1,2-a]pyridine, or
2-(3,4-dimethoxy-phenyl)-6-methyl-imidazo[1,2-a]pyridine.

Also preferred for the above mentioned use are compounds of formula I, in which A signifies unsubstituted heteroaryl or heteroaryl substituted with one or more substituents

selected from the group consisting of (C_{1-6})-alkyl, halogen, halogen-(C_{1-6})-alkyl, hydroxy, (C_{1-6})-alkoxy, benzyloxy, amino, (C_{1-6})-alkylamino, di-(C_{1-6})-alkylamino, arylamino, diarylamino or nitro.

The following are examples of such compounds:
2-benzofuran-2-yl-imidazo[1,2-a]pyridine,
2-benzo[b]thiophen-3-yl-imidazo[1,2-a]pyridine,
2-(5-methyl-thiophen-2-yl)-imidazo[1,2-a]pyridine, or
2-(2,5-dimethyl-thiophen-3-yl)-imidazo[1,2-a]pyridine.

Preferred compounds of formula I for the above mentioned use are also those, in which A signifies the group



wherein X is, independently from each other, $-CH_2-$ or -O-; and n is 1 or 2.

The following are examples of such compounds:
2-indan-5-yl-imidazo[1,2-a]pyridine,
2-(2,3-dihydro-benzofuran-5-yl)-imidazo[1,2-a]pyridine, or
2-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-imidazo[1,2-a]pyridine.

Another object of the present invention are novel compounds of formula I, which are
7-chloro-2-(3,4-dimethyl-phenyl)-imidazo[1,2-a]pyridine,
2-(3,4-dimethoxy-phenyl)-imidazo[1,2-a]pyridine,
2-(3,4-dimethyl-phenyl)-7-methoxy-imidazo[1,2-a]pyridine,
2-(3,4-dimethoxy-phenyl)-7-methoxy-imidazo[1,2-a]pyridine,
2-(3,4-dimethyl-phenyl)-7-methyl-imidazo[1,2-a]pyridine,
2-(3-bromo-4-fluoro-phenyl)-imidazo[1,2-a]pyridine,
2-(4-benzyloxy-3-methoxy-phenyl)-imidazo[1,2-a]pyridine,
2-indan-5-yl-imidazo[1,2-a]pyridine,
2-(3-bromo-phenyl)-imidazo[1,2-a]pyridine,
2-(3-iodo-phenyl)-imidazo[1,2-a]pyridine,
2-(3-methyl-phenyl)-imidazo[1,2-a]pyridine,
2-benzo[b]thiophen-3-yl-imidazo[1,2-a]pyridine,
2-(3-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine,
2-(2,3-dihydro-benzofuran-5-yl)-imidazo[1,2-a]pyridine,
2-(3-fluoro-phenyl)-imidazo[1,2-a]pyridine,
2-(3,4-dimethyl-phenyl)-7-ethyl-imidazo[1,2-a]pyridine,

2-(5-methyl-thiophen-2-yl)-imidazo[1,2-a]pyridine,
2-(2,5-dimethyl-thiophen-3-yl)-imidazo[1,2-a]pyridine, or
2-(3,4-dimethoxy-phenyl)-6-methyl-imidazo[1,2-a]pyridine.

A further object of the present invention are medicaments containing one or more of these novel compounds, namely 7-chloro-2-(3,4-dimethyl-phenyl)-imidazo[1,2-a]pyridine, 2-(3,4-dimethoxy-phenyl)-imidazo[1,2-a]pyridine, 2-(3,4-dimethyl-phenyl)-7-methoxy-imidazo[1,2-a]pyridine, 2-(3,4-dimethoxy-phenyl)-7-methoxy-imidazo[1,2-a]pyridine, 2-(3,4-dimethyl-phenyl)-7-methyl-imidazo[1,2-a]pyridine, 2-(3-bromo-4-fluoro-phenyl)-imidazo[1,2-a]pyridine, 2-(4-benzyloxy-3-methoxy-phenyl)-imidazo[1,2-a]pyridine, 2-indan-5-yl-imidazo[1,2-a]pyridine, 2-(3-bromo-phenyl)-imidazo[1,2-a]pyridine, 2-(3-iodo-phenyl)-imidazo[1,2-a]pyridine, 2-(3-methyl-phenyl)-imidazo[1,2-a]pyridine, 2-benzo[b]thiophen-3-yl-imidazo[1,2-a]pyridine, 2-(3-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine, 2-(2,3-dihydro-benzofuran-5-yl)-imidazo[1,2-a]pyridine, 2-(3-fluoro-phenyl)-imidazo[1,2-a]pyridine, 2-(3,4-dimethyl-phenyl)-7-ethyl-imidazo[1,2-a]pyridine, 2-(5-methyl-thiophen-2-yl)-imidazo[1,2-a]pyridine, 2-(2,5-dimethyl-thiophen-3-yl)-imidazo[1,2-a]pyridine, or 2-(3,4-dimethoxy-phenyl)-6-methyl-imidazo[1,2-a]pyridine, and pharmaceutically acceptable excipients.

The compounds of formula I and their pharmaceutically acceptable salts are, as already mentioned above, metabotropic glutamate receptor antagonists and can be used for the treatment or prevention of mGluR5 receptor mediated disorders, such as acute and/or chronic neurological disorders, cognitive disorders and memory deficits, as well as acute and chronic pain. Treatable neurological disorders are for instance epilepsy, schizophrenia, anxiety, acute, traumatic or chronic degenerative processes of the nervous system, such as Alzheimer's disease, senile dementia, Huntington's chorea, ALS, multiple sclerosis, dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficient functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, psychoses, opiate addiction, anxiety, vomiting, dyskinesia and depression. Other treatable indications are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia.

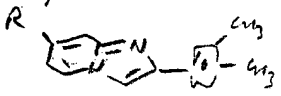
The compounds of formula I and their pharmaceutically acceptable salts are especially useful as analgesics. Treatable kinds of pain include inflammatory pain auch as arthritis and rheumatoid disease, vasculitis, neuropathic pain such as trigeminal or herpetic neuralgia, diabetic neuropathy pain, causalgia, hyperalgesia, severe chronic pain, post-operative pain and pain associated with various conditions like cancer, angina, renal or billiay colic, menstruation, migraine and gout.

The pharmacological activity of the compounds was tested using the following methods:

cDNA encoding rat mGlu 5a receptor was transiently transfected into EBNA cells using a procedure described by E.-J. Schlaeger and K. Christensen (Transient gene expression in mammalian cells grown in serum-free suspension culture, *Cytotechnology* 1999, 30, 71-83). $[Ca^{2+}]i$ measurements were performed on mGlu 5a transfected EBNA cells after incubation of the cells with Fluo 3-AM (obtainable by FLUKA, 0.5 µM final concentration) for 1 hour at 37 °C followed by 4 washes with assay buffer (DMEM supplemented with Hank's salt and 20 mM HEPES. $[Ca^{2+}]i$ measurements were done using a fluorometric imaging plate reader (FLIPR, Molecular Devices Corporation; La Jolla, CA, USA). When compounds were evaluated as antagonists they were tested against 10 µM glutamate as agonist.

The inhibition (antagonists) curves were fitted with a four parameter logistic equation giving IC_{50}, and Hill coefficient using the iterative non linear curve fitting software Origin (Microcal Software Inc., Northampton, MA, USA).

The compounds of the present invention are mGluR 5a receptor antagonists. In the following table the activities of compounds of formula I as measured in the assay described above are shown:



Ex.	Activity [µM]
1	0.1
2	1.88
3	6.8
4	0.14
5	3.3
6	0.037
7	0.28
8	0.69
9	0.83
10	0.93
11	0.95
12	0.97
13	1.23
14	1.55
15	1.66
16	2.76
17	2.79
18	2.86
19	3.41
20	3.64
21	6.13
22	7.5

• R = O CH_3

• H ← fare !

• CH_3

S1 : Barbara !!, 500 mg

5/2/03

Ex.	Activity [μM]
23	8.77
24	0.58
25	1.65
26	8.3
27	0.99
28	10
29	10

The affinity of compounds of general formula I to the central benzodiazepine receptors *in vitro* was also tested using standard methods as for example described in *Nature* 1981, *294*, 763-765 and *J. Neurochemistry* 1981, *37*, 714-722. According to these methods, the inhibition of the binding of tritiated flumazenil to the specific benzodiazepine receptors in the cortex of rats by the respective test substances is determined and the inhibition dissociation constant (Ki) of each test compound is determined according to the method of Cheng & Prusoff (1973).

Ex 6 2-(3,4-Dimethyl-phenyl)-imidazo[1,2-a]pyridine hydrochloride was tested according to this method and showed a pKi (negative logarithm of the Ki) of 5.2, i.e. the compound does not possess good affinity towards the benzodiazepine receptors.

The compounds of formula I and pharmaceutically acceptable salts thereof can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. However, the administration can also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I and pharmaceutically acceptable salts thereof can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Adjuvants, such as alcohols, polyols, glycerol, vegetable oils and the like, can be used for aqueous injection solutions of water-soluble salts of compounds of formula I, but as a rule are not necessary.

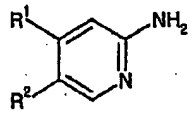
Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

In addition, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

As mentioned earlier, medicaments containing a compound of formula IA or IB or pharmaceutically acceptable salts thereof and a therapeutically inert excipient are also an object of the present invention, as is a process for the production of such medicaments which comprises bringing one or more compounds of formula IA or IB or pharmaceutically acceptable salts thereof and, if desired, one or more other therapeutically valuable substances into a galenical dosage form together with one or more therapeutically inert carriers.

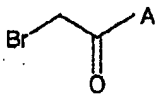
The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, the effective dosage for oral or parenteral administration is between 0.01-20 mg/kg/day, with a dosage of 0.1-10 mg/ kg/day being preferred for all of the indications described. The daily dosage for an adult human being weighing 70 kg accordingly lies between 0.7-1400 mg per day, preferably between 7 and 700 mg per day.

The compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods well known to those of ordinary skill in the art. For example, compounds of formula I can be obtained by reacting a compound of the formula



II

with an α-bromo ketone of formula



III

wherein R^1, R^2 and A have the significances as defined before, and if desired, converting a compounds of formulas I into a pharmaceutically acceptable salt.

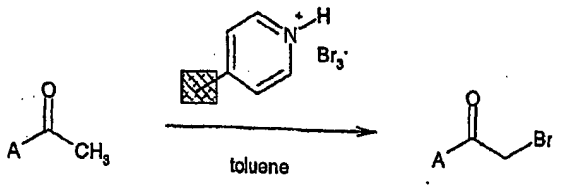
This reaction is for example described in *J. Org. Chem.* 1954, 19, 1370-1374 or in *J. Heterocyclic Chem.* 1988, 25, 129-137. The cyclocondensation of 2-amino pyridines with

α-bromo ketones is carried out in a polar solvent like ethanol and heated under reflux conditions for several hours or, alternatively, the reactants are dissolved in a solvent like acetone at room temperature.

The preparation of compounds of formula II is well known to those skilled in the art and some of the compounds of formula II are commercially available. Reviews for the synthesis of 2-aminopyridines can be found in M. T. Leffler, *Organic Reactions*, Vol. 1, Ed. R. Adams, J. Wiley and Sons, NY, 1942, Ch. 4, pp. 91-104, or in A. S. Tomcufcik, L. N. Starker, *The Chemistry of Heterocyclic Compounds, Pyridine and its Derivatives*, Part 3, Ed. E. Klingsberg, Interscience, NY, 1962, Ch. IX, pp. 1-177, or in E. F. V. Scriven, *Comprehensive Heterocyclic Chemistry*, Vol. 2, Part 2A, Eds. A. J. Boulton and A. McKillop, Pergamon Press, NY, 1984, Ch. 2.05, pp. 165-314. For instance, these compounds can be prepared by the Chichibabin reaction involving the reaction of a substituted pyridine derivative with sodium amide or sodium amide in the presence of a substituted amine to yield a 2-aminopyridine derivative of formula II.

The compounds of formula III are also commercially available or can be easily prepared by the method as described in *J. Chem. Soc., Perkin Trans. 1*, 1999, 2425-2427. For example, 2-bromo-1-(3-bromo-4-fluoro-phenyl)-ethanone, 1-(4-benzyloxy-3-methoxy-phenyl)-2-bromo-ethanone, 2-bromo-1-indan-5-yl-ethanone, 2-iodo-1-(3-bromo-phenyl)-ethanone, 2-bromo-1-m-tolyl-ethanone, 2-bromo-1-(3-trifluoromethyl-phenyl)-ethanone, 2-bromo-1-(2,3-dihydro-benzofuran-5-yl)-ethanone, 2-bromo-1-(3,4-dimethyl-phenyl)-ethanone, 2-bromo-1-(5-methyl-thiophen-2-yl)-ethanone, 2-bromo-1-(3-methoxy-phenyl)-propan-1-one, 2-bromo-1-(2,5-dimethyl-thiophen-3-yl)-ethanone, 2-bromo-1-(3,4-dimethoxy-phenyl)-ethanone, 2-bromo-1-(4-morpholin-4-yl-3-nitro-phenyl)-ethanone and 2-bromo-1-(3,4-dimethyl-phenyl)-hexan-1-one are obtained in analogy to this method by α-bromination of the appropiate commercially available acetophenones using polymer-supported pyridinium bromide perbromide (PSPBP) in toluene at 10 °C (scheme 1).

Scheme 1



IV III

The preparation of compounds of formula I, especially of the novel compounds 7-chloro-2-(3,4-dimethyl-phenyl)-imidazo[1,2-a]pyridine, 2-(3,4-dimethoxy-phenyl)-

imidazo[1,2-a]pyridine, 2-(3,4-dimethyl-phenyl)-7-methoxy-imidazo[1,2-a]pyridine, 2-(3,4-dimethoxy-phenyl)-7-methoxy-imidazo[1,2-a]pyridine, 2-(3,4-dimethyl-phenyl)-7-methyl-imidazo[1,2-a]pyridine, 2-(3-bromo-4-fluoro-phenyl)-imidazo[1,2-a]pyridine, 2-(4-benzyloxy-3-methoxy-phenyl)-imidazo[1,2-a]pyridine, 2-indan-5-yl-imidazo[1,2-a]pyridine, 2-(3-bromo-phenyl)-imidazo[1,2-a]pyridine, 2-(3-iodo-phenyl)-imidazo[1,2-a]pyridine, 2-(3-methyl-phenyl)-imidazo[1,2-a]pyridine, 2-benzo[b]thiophen-3-yl-imidazo[1,2-a]pyridine, 2-(3-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine, 2-(2,3-dihydro-benzofuran-5-yl)-imidazo[1,2-a]pyridine, 2-(3-fluoro-phenyl)-imidazo[1,2-a]pyridine, 2-(3,4-dimethyl-phenyl)-7-ethyl-imidazo[1,2-a]pyridine, 2-(5-methyl-thiophen-2-yl)-imidazo[1,2-a]pyridine, 2-(2,5-dimethyl-thiophen-3-yl)-imidazo[1,2-a]pyridine, or 2-(3,4-dimethoxy-phenyl)-6-methyl-imidazo[1,2-a]pyridine, is described in more detail in the following examples. The examples are to be considered as being illustrative and representative of the invention, but not as limiting the scope of the present invention.

Pharmaceutically acceptable salts of coumpounds of formula I can be manufactured readily according to methods known per se and taking into consideration the nature of the compound to be converted into a salt. Inorganic or organic acids such as, for example, hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid or citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like are suitable for the formation of pharmaceutically acceptable salts of basic compounds of formula I. Compounds which contain the alkali metals or alkaline earth metals, for example sodium, potassium, calcium, magnesium or the like, basic amines or basic amino acids are suitable for the formation of pharmaceutically acceptable salts of acidic compounds.

Example 1

7-Chloro-2-(3,4-dimethyl-phenyl)-imidazo[1,2-a]pyridine

To a stirred solution of 2-amino-4-chloro-pyridine (0.39 g, 3.03 mmol) in ethanol (25 ml) was added 3,4-dimethyl-phenacylbromide (0.69 g, 3.03 mmol). The reaction mixture was stirred under reflux conditions for 16 h, poured into sat. $NaHCO_3$ solution (70 ml) and extracted with dichloromethane (70 ml). The combined organic layers were washed with brine (70 ml), dried ($MgSO_4$) and evaporated to give the crude product as a brown solid (0.84 g). Further purification by column chromatography on silica gel (ethyl acetate/toluene 1:9) and crystallization from ethyl acetate/hexane yielded the title compound (0.54 g, 69%) as a pale yellow solid, m.p. 144 °C and MS: m/e = 256.2 (M^+).

Example 2

2-(3,4-Dimethoxy-phenyl)-7-methyl-imidazo[1,2-a]pyridine

The title compound, pale yellow solid, m.p. 163 °C and MS: m/e = 268.1 (M^+), was prepared in accordance with the general method of example 1 from 2-amino-4-methyl-pyridine and 3,4-dimethoxy-phenacylbromide.

Example 3

2-(3,4-Dimethoxy-phenyl)-imidazo[1,2-a]pyridine

The title compound, pale yellow solid, m.p. 96 °C and MS: m/e = 254.1 (M^+), was prepared in accordance with the general method of example 1 from 2-amino-pyridine and 3,4-dimethoxy-phenacylbromide.

Example 4

2-(3,4-Dimethyl-phenyl)-7-methoxy-imidazo[1,2-a]pyridine

The title compound, pale yellow solid, m.p. 175 °C and MS: m/e = 252.2 (M^+), was prepared in accordance with the general method of example 1 from 2-amino-4-methoxy-pyridine and 3,4-dimethyl-phenacylbromide.

Example 5

2-(3,4-Dimethoxy-phenyl)-7-methoxy-imidazo[1,2-a]pyridine

The title compound, pale yellow solid, m.p. 142 °C and MS: m/e = 284.1 (M^+), was prepared in accordance with the general method of example 1 from 2-amino-4-methoxy-pyridine and 3,4-dimethoxy-phenacylbromide.

Example 6

2-(3,4-Dimethyl-phenyl)-imidazo[1,2-a]pyridine hydrochloride

The title compound was obtained in analogy to the method as described in patent application WO 00/08021.

Example 7

2-(3,4-Dimethyl-phenyl)-7-methyl-imidazo[1,2-a]pyridine

The title compound, solid, MS: m/e = 237.0 ($M+H^+$), was obtained in analogy to the general method of example 1.

Example 8

2-(3-Bromo-4-fluoro-phenyl)-imidazo[1,2-a]pyridine

In analogy to the method as described in *J. Heterocyclic Chem.* 1988, *25*, 129-137, 2-Bromo-1-(3-bromo-4-fluoro-phenyl)-ethanone (89mg, 0.3mmol) and 2-Aminopyridine (28mg, 0.3mmol) were dissolved in 2ml of acetone and shaken overnight. The solvent was evaporated and and the residue was dissolved in 1ml of DMF. The title compound (m/e = 292.6, $[M+H^+]$) was isolated from this solution by HPLC chromatography (YMC CombiPrep C18 column 50x20mm, solvent gradient 10-95% CH_3CN in 0.1% TFA(aq) over 6.0min, λ = 230nm, flow rate 40ml/min).

Example 9

2-(4-Benzyloxy-3-methoxy-phenyl)-imidazo[1,2-a]pyridine

The title compound, MS: m/e = 330.9 ($M+H^+$), was prepared in accordance with the general method of example 8 from 1-(4-Benzyloxy-3-methoxy-phenyl)-2-bromo-ethanone.

Example 10

2-Indan-5-yl-imidazo[1,2-a]pyridine

The title compound, MS: m/e = 234.8 ($M+H^+$), was prepared in accordance with the general method of example 8 from 2-Bromo-1-indan-5-yl-ethanone.

Example 11

2-(3-Bromo-phenyl)-imidazo[1,2-a]pyridine

The title compound, MS: m/e = 274.5 ($M+H^+$) was prepared in accordance with the general method of example 8 from 2-Bromo-1-(3-bromo-phenyl)-ethanone.

Example 12

2-(3-Iodo-phenyl)-imidazo[1,2-a]pyridine

The title compound, MS: m/e = 320.7 ($M+H^+$), was prepared in accordance with the general method of example 8 from 2-Iodo-1-(3-bromo-phenyl)-ethanone.

Example 13

2-(3-Chloro-phenyl)-imidazo[1,2-a]pyridine

The title compound, MS: m/e = 228.5 ($M+H^+$), was prepared in accordance with the general method of example 8 from 2-Chloro-1-(3-bromo-phenyl)-ethanone.

Example 14

2-(3-Methyl-phenyl)-imidazo[1,2-a]pyridine

The title compound, MS: m/e = 208.8 ($M+H^+$), was prepared in accordance with the general method of example 8 from 2-Bromo-1-*m*-tolyl-ethanone.

Example 15

2-Benzofuran-2-yl-imidazo[1,2-a]pyridine

The title compound, MS: m/e = 234.8 ($M+H^+$), was prepared in accordance with the general method of example 8 from 1-Benzofuran-2-yl-2-bromo-ethanone.

Example 16

2-Benzo[b]thiophen-3-yl-imidazo[1,2-a]pyridine

The title compound, MS: m/e = 250.8 ($M+H^+$), was prepared in accordance with the general method of example 8 from 1-Benzo[b]thiophen-3-yl-2-bromo-ethanone.

Example 17

2-(3-Trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine

The title compound, MS: m/e = 262.7 ($M+H^+$) was prepared in accordance with the general method of example 8 from 2-Bromo-1-(3-trifluoromethyl-phenyl)-ethanone.

Example 18

2-(2,3-Dihydro-benzofuran-5-yl)-imidazo[1,2-a]pyridine

The title compound, MS: m/e = 236.8 ($M+H^+$), was prepared in accordance with the general method of example 8 from 2-Bromo-1-(2,3-dihydro-benzofuran-5-yl)-ethanone.

Example 19

2-(3-Fluoro-phenyl)-imidazo[1,2-a]pyridine

The title compound, MS: m/e = 212.7 ($M+H^+$), was prepared in accordance with the general method of example 8 from 2-Bromo-1-(3-fluoro-phenyl)-ethanone.

Example 20

2-(3,4-Dimethyl-phenyl)-7-ethyl-imidazo[1,2-a]pyridine

The title compound, MS: m/e = 250.8 ($M+H^+$), was prepared in accordance with the general method of example 8 from 2-Bromo-1-(3,4-dimethyl-phenyl)-ethanone and 4-Ethyl-pyridin-2-ylamine.

Example 21

2-(5-Methyl-thiophen-2-yl)-imidazo[1,2-a]pyridine

The title compound, MS: m/e = 215.0 ($M+H^+$), was prepared in accordance with the general method of example 8 from 2-Bromo-1-(5-methyl-thiophen-2-yl)-ethanone.

Example 22

7-Methyl-2-phenyl-imidazo[1,2-a]pyridine

The title compound, MS: m/e = 209.0 ($M+H^+$), was obtained by the method as described in *J. Med. Chem.* 1998, *41(25)*, 5108-5112.

Example 23

2-(4-Methyl-phenyl)-imidazo[1,2-a]pyridine

The title compound, MS: m/e = 209.2 ($M+H^+$), was obtained by the method as described in patent application EP 0 533 058.

Example 24

2-(2,5-Dimethyl-thiophen-3-yl)-imidazo[1,2-a]pyridine

The title compound, MS: m/e = 229.0 ($M+H^+$), was prepared in accordance with the general method of example 8 from 2-bromo-1-(2,5-dimethyl-thiophen-3-yl)-ethanone.

Example 25

2-(3-Methoxy-phenyl)-imidazo[1,2-a]pyridine

The title compound, MS: m/e = 224.8 ($M+H^+$), was prepared in accordance with the general method of example 8 from 2-bromo-1-(3-methoxy-phenyl)-ethanone.

Example 26

2-(3,4-Dimethoxy-phenyl)-6-methyl-imidazo[1,2-a]pyridine

The title compound, MS: m/e = 269.2 ($M+H^+$), was prepared in accordance with the general method of example 8 from 5-methyl-pyridin-2-ylamine and 2-bromo-1-(3,4-dimethoxy-phenyl)-ethanone.

Example 27

2-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-imidazo[1,2-a]pyridine

The title compound, MS: m/e = 253.0 ($M+H^+$), was prepared in accordance with the general method of example 8 from 2-bromo-1-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-ethanone.

Example 28

6-Methyl-2-(4-methyl-phenyl)-imidazo[1,2-a]pyridine

The title compound, MS: m/e = 223.0 ($M+H^+$), was obtained by the method as described in patent application EP 1 038 875.

Example 29

2-(3-Nitro-phenyl)-imidazo[1,2-a]pyridine

The title compound, MS: m/e = 240.2 ($M+H^+$), was prepared in accordance with the general method of example 8 from 2-bromo-1-(3-nitro-phenyl)-ethanone.

Example A

Tablets of the following composition are produced in a conventional manner:

	mg/Tablet
Active ingredient	100
Powdered. lactose	95
White corn starch	35
Polyvinylpyrrolidone	8
Na carboxymethylstarch	10
Magnesium stearate	2
Tablet weight	250

Example B

Tablets of the following composition are produced in a conventional manner:

	mg/Tablet
Active ingredient	200
Powdered. lactose	100
White corn starch	64
Polyvinylpyrrolidone	12
Na carboxymethylstarch	20
Magnesium stearate	4
Tablet weight	400

Example C

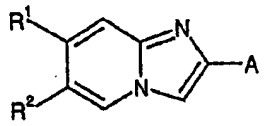
Capsules of the following composition are produced:

	mg/Capsule
Active ingredient	50
Crystalline. lactose	60
Microcrystalline cellulose	34
Talc	5
Magnesium stearate	1
Capsule fill weight	150

The active ingredient having a suitable particle size, the crystalline lactose and the microcrystalline cellulose are homogeneously mixed with one another, sieved and thereafter talc and magnesium stearate are admixed. The final mixture is filled into hard gelatine capsules of suitable size.

Claims

1. The use of a compound of the general formula



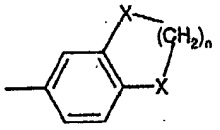
I

wherein

R^1 signifies hydrogen, (C_{1-6})-alkyl, halogen, hydroxy, (C_{1-6})-alkoxy;

R^2 signifies hydrogen, (C_{1-6})-alkyl, halogen, hydroxy, (C_{1-6})-alkoxy; and

A signifies unsubstituted aryl or aryl substituted with one or more substituents selected from the group consisting of (C_{1-6})-alkyl, halogen, halogen-(C_{1-6})-alkyl, hydroxy, (C_{1-6})-alkoxy, benzyloxy, amino, (C_{1-6})-alkylamino, di-(C_{1-6})-alkyl-amino, arylamino, diarylamino or nitro, or signifies unsubstituted heteroaryl or heteroaryl substituted with one or more substituents selected from the group consisting of (C_{1-6})-alkyl, halogen, halogen-(C_{1-6})-alkyl, hydroxy, (C_{1-6})-alkoxy, benzyloxy, amino, (C_{1-6})-alkylamino, di-(C_{1-6})-alkyl-amino, arylamino, diarylamino or nitro or signifies the group



wherein

X is, independently from each other, $-CH_2-$ or -O-; and

n is 1 or 2;

and their pharmaceutically acceptable salts for the manufacture of medicaments for the treatment or prevention of mGluR5 receptor mediated disorders.

2. The use of a compound according to claim 1 for the manufacture of medicaments for the treatment and prevention of acute and/or chronic neurological disorders, cognitive disorders and memory deficits such as Alzheimer's disease, senile dementia, Parkinson's disease, ischemia, Huntington's chorea, amyotrophic lateral sclerosis and multiple sclerosis, psychiatric diseases such as psychosis, epilepsy, schizophrenia, anxiety and depression.

3. The use of a compound according to claim 1 for the manufacture of medicaments for the treatment and prevention of acute and/or chronic pain.

4. The use of a compound according to claim 1, wherein A signifies unsubstituted aryl or aryl substituted with one or more substituents selected from the group consisting of (C_{1-6})-alkyl, halogen, halogen-(C_{1-6})-alkyl, hydroxy, (C_{1-6})-alkoxy, benzyloxy, amino, (C_{1-6})-alkylamino, di-(C_{1-6})-alkyl-amino, arylamino, diarylamino or nitro, and R^1 and R^2 have the significances as defined in claim1.

5. The use of a compound according to claim 4, wherein A signifies unsubstituted phenyl or phenyl substituted with one or more substituents selected from the group consisting of (C_{1-6})-alkyl, halogen, halogen-(C_{1-6})-alkyl, hydroxy, (C_{1-6})-alkoxy, benzyloxy, amino, (C_{1-6})-alkylamino, di-(C_{1-6})-alkyl-amino, arylamino, diarylamino or nitro.

6. The use of a compound according to claim 5, wherein A signifies phenyl substituted with one substituent selected from the group consisting of (C_{1-6})-alkyl, halogen, halogen-(C_{1-6})-alkyl, hydroxy, (C_{1-6})-alkoxy, benzyloxy, amino, (C_{1-6})-alkylamino, di-(C_{1-6})-alkyl-amino, arylamino, diarylamino or nitro.

7. The use of a compound according to claim 6, which compound is selected from the group consisting of
2-(3-bromo-phenyl)-imidazo[1,2-a]pyridine,
2-(3-iodo-phenyl)-imidazo[1,2-a]pyridine,
2-(3-chloro-phenyl)-imidazo[1,2-a]pyridine,
2-(3-methyl-phenyl)-imidazo[1,2-a]pyridine,
2-(3-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine,
2-(3-fluoro-phenyl)-imidazo[1,2-a]pyridine,
7-methyl-2-phenyl-imidazo[1,2-a]pyridine,
2-(4-methyl-phenyl)-imidazo[1,2-a]pyridine,
2-(3-methoxy-phenyl)-imidazo[1,2-a]pyridine,
6-methyl-2-(4-methyl-phenyl)-imidazo[1,2-a]pyridine, or
2-(3-nitro-phenyl)-imidazo[1,2-a]pyridine.

8. The use of a compound according to claim 5, wherein A signifies phenyl substituted with at least two substituents selected from the group consisting of (C_{1-6})-alkyl, halogen, halogen-(C_{1-6})-alkyl, hydroxy, (C_{1-6})-alkoxy, benzyloxy, amino, (C_{1-6})-alkylamino, di-(C_{1-6})-alkyl-amino, arylamino, diarylamino or nitro.

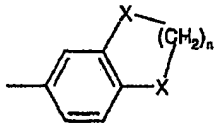
9. The use of a compound according to claim 8, which compound is selected from the group consisting of
7-chloro-2-(3,4-dimethyl-phenyl)-imidazo[1,2-a]pyridine,
2-(3,4-dimethoxy-phenyl)-7-methyl-imidazo[1,2-a]pyridine,
2-(3,4-dimethoxy-phenyl)-imidazo[1,2-a]pyridine,
2-(3,4-dimethyl-phenyl)-7-methoxy-imidazo[1,2-a]pyridine,

2-(3,4-dimethoxy-phenyl)-7-methoxy-imidazo[1,2-a]pyridine,
2-(3,4-dimethyl-phenyl)-imidazo[1,2-a]pyridine hydrochloride,
2-(3,4-dimethyl-phenyl)-7-methyl-imidazo[1,2-a]pyridine,
2-(3-bromo-4-fluoro-phenyl)-imidazo[1,2-a]pyridine,
2-(4-benzyloxy-3-methoxy-phenyl)-imidazo[1,2-a]pyridine,
2-(3,4-dimethyl-phenyl)-7-ethyl-imidazo[1,2-a]pyridine, or
2-(3,4-dimethoxy-phenyl)-6-methyl-imidazo[1,2-a]pyridine.

10. The use of a compound according to claim 1, wherein A signifies unsubstituted heteroaryl or heteroaryl substituted with one or more substituents selected from the group consisting of (C_{1-6})-alkyl, halogen, halogen-(C_{1-6})-alkyl, hydroxy, (C_{1-6})-alkoxy, benzyloxy, amino, (C_{1-6})-alkylamino, di-(C_{1-6})-alkyl-amino, arylamino, diarylamino or nitro.

11. The use of a compound according to claim 10, which compound is selected from the group consisting of
2-benzofuran-2-yl-imidazo[1,2-a]pyridine,
2-benzo[b]thiophen-3-yl-imidazo[1,2-a]pyridine,
2-(5-methyl-thiophen-2-yl)-imidazo[1,2-a]pyridine, or
2-(2,5-dimethyl-thiophen-3-yl)-imidazo[1,2-a]pyridine.

12. The use of a compound according to claim 1, wherein A signifies the group



wherein X is, independently from each other, $-CH_2-$ or -O-; and n is 1 or 2.

13. The use of a compound according to claim 12, which compound is selected from the group consisting of
2-indan-5-yl-imidazo[1,2-a]pyridine,
2-(2,3-dihydro-benzofuran-5-yl)-imidazo[1,2-a]pyridine, or
2-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-imidazo[1,2-a]pyridine.

14. A compound of formula I of claim 1, which compound is selected from the group consisting of
7-Chloro-2-(3,4-dimethyl-phenyl)-imidazo[1,2-a]pyridine,
2-(3,4-dimethoxy-phenyl)-imidazo[1,2-a]pyridine,
2-(3,4-dimethyl-phenyl)-7-methoxy-imidazo[1,2-a]pyridine,
2-(3,4-dimethoxy-phenyl)-7-methoxy-imidazo[1,2-a]pyridine,
2-(3,4-dimethyl-phenyl)-7-methyl-imidazo[1,2-a]pyridine,

2-(3-bromo-4-fluoro-phenyl)-imidazo[1,2-a]pyridine,
2-(4-benzyloxy-3-methoxy-phenyl)-imidazo[1,2-a]pyridine,
2-indan-5-yl-imidazo[1,2-a]pyridine,
2-(3-bromo-phenyl)-imidazo[1,2-a]pyridine,
2-(3-iodo-phenyl)-imidazo[1,2-a]pyridine,
2-(3-methyl-phenyl)-imidazo[1,2-a]pyridine,
2-benzo[b]thiophen-3-yl-imidazo[1,2-a]pyridine,
2-(3-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine,
2-(2,3-dihydro-benzofuran-5-yl)-imidazo[1,2-a]pyridine,
2-(3-fluoro-phenyl)-imidazo[1,2-a]pyridine,
2-(3,4-dimethyl-phenyl)-7-ethyl-imidazo[1,2-a]pyridine,
2-(5-methyl-thiophen-2-yl)-imidazo[1,2-a]pyridine,
2-(2,5-dimethyl-thiophen-3-yl)-imidazo[1,2-a]pyridine, or
2-(3,4-dimethoxy-phenyl)-6-methyl-imidazo[1,2-a]pyridine.

15. A medicament containing one or more compounds selected from the group consisting of 7-chloro-2-(3,4-dimethyl-phenyl)-imidazo[1,2-a]pyridine, 2-(3,4-dimethoxy-phenyl)-imidazo[1,2-a]pyridine, 2-(3,4-dimethyl-phenyl)-7-methoxy-imidazo[1,2-a]pyridine, 2-(3,4-dimethoxy-phenyl)-7-methoxy-imidazo[1,2-a]pyridine, 2-(3,4-dimethyl-phenyl)-7-methyl-imidazo[1,2-a]pyridine, 2-(3-bromo-4-fluoro-phenyl)-imidazo[1,2-a]pyridine, 2-(4-benzyloxy-3-methoxy-phenyl)-imidazo[1,2-a]pyridine, 2-indan-5-yl-imidazo[1,2-a]pyridine, 2-(3-bromo-phenyl)-imidazo[1,2-a]pyridine, 2-(3-iodo-phenyl)-imidazo[1,2-a]pyridine, 2-(3-methyl-phenyl)-imidazo[1,2-a]pyridine, 2-benzo[b]thiophen-3-yl-imidazo[1,2-a]pyridine, 2-(3-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine, 2-(2,3-dihydro-benzofuran-5-yl)-imidazo[1,2-a]pyridine, 2-(3-fluoro-phenyl)-imidazo[1,2-a]pyridine, 2-(3,4-dimethyl-phenyl)-7-ethyl-imidazo[1,2-a]pyridine, 2-(5-methyl-thiophen-2-yl)-imidazo[1,2-a]pyridine, 2-(2,5-dimethyl-thiophen-3-yl)-imidazo[1,2-a]pyridine, or 2-(3,4-dimethoxy-phenyl)-6-methyl-imidazo[1,2-a]pyridine, and pharmaceutically acceptable excipients.

16. A medicament containing one or more compounds as claimed in claim 1 and pharmaceutically acceptable excipients for the treatment and prevention of acute and/or chronic neurological disorders, cognitive disorders and memory deficits such as Alzheimer's disease, senile dementia, Parkinson's disease, ischemia, Huntington's chorea, amyotrophic lateral sclerosis and multiple sclerosis, psychiatric diseases such as psychosis, epilepsy, schizophrenia, anxiety and depression, or acute and/or chronic pain.

17. A compound selected from the group consisting of 7-chloro-2-(3,4-dimethyl-phenyl)-imidazo[1,2-a]pyridine, 2-(3,4-dimethoxy-phenyl)-imidazo[1,2-a]pyridine, 2-(3,4-dimethyl-phenyl)-7-methoxy-imidazo[1,2-a]pyridine, 2-(3,4-dimethoxy-phenyl)-7-

methoxy-imidazo[1,2-a]pyridine, 2-(3,4-dimethyl-phenyl)-7-methyl-imidazo[1,2-a]pyridine, 2-(3-bromo-4-fluoro-phenyl)-imidazo[1,2-a]pyridine, 2-(4-benzyloxy-3-methoxy-phenyl)-imidazo[1,2-a]pyridine, 2-indan-5-yl-imidazo[1,2-a]pyridine, 2-(3-bromo-phenyl)-imidazo[1,2-a]pyridine, 2-(3-iodo-phenyl)-imidazo[1,2-a]pyridine, 2-(3-methyl-phenyl)-imidazo[1,2-a]pyridine, 2-benzo[b]thiophen-3-yl-imidazo[1,2-a]pyridine, 2-(3-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine, 2-(2,3-dihydro-benzofuran-5-yl)-imidazo[1,2-a]pyridine, 2-(3-fluoro-phenyl)-imidazo[1,2-a]pyridine, 2-(3,4-dimethyl-phenyl)-7-ethyl-imidazo[1,2-a]pyridine, 2-(5-methyl-thiophen-2-yl)-imidazo[1,2-a]pyridine, 2-(2,5-dimethyl-thiophen-3-yl)-imidazo[1,2-a]pyridine, or 2-(3,4-dimethoxy-phenyl)-6-methyl-imidazo[1,2-a]pyridine, as well as their pharmaceutically acceptable salts, for the treatment or prevention of diseases.

18. The invention as hereinbefore described.

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INTERNATIONAL SEARCH REPORT

Intel onal Application No
PCT/EP 02/03098

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/437 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BARLIN, GORDON B.: "Imidazo'1,2-b!pyridazines: syntheses and interaction with central and peripheral-type (mitochondrial) benzodiazepine receptors" JOURNAL OF HETEROCYCLIC CHEMISTRY (1998), 35(5), 1205-1217 , XP001105493 abstract examples 198,201; table 1 --- -/--	2,4-9, 14-17

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 October 2002	23/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Economou, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/03098

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ALMIRANTE, LUIGI ET AL: "Derivatives of imidazole. I. Synthesis and reactions of imidazo'1,2-a!pyridines with analgesic, antiinflammatory, antipyretic, an anticonvulsant activity" J. MED. CHEM. (1965), 8(3), 305-12, XP001106084 example 5; table 1 page 311, left-hand column, paragraph 3	2,4-9, 14-17
P,X	WO 01 74815 A (ORTHO MCNEIL PHARMACEUTICAL, INC., USA) 11 October 2001 (2001-10-11) examples 8,10-26,30,33-41,52 claims 28,29,32	2,4-17
A	WO 91 19497 A (SMITHKLINE BEECHAM CORP) 26 December 1991 (1991-12-26) the whole document	2-17

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,4-15,17 (incomplete)

The subject-matter of present claim 1 is defined by means of the functional feature "mGluR5 receptor mediated disorders". Hence, the disorders to be treated/prevented are defined by the mechanism of action of the claimed compounds. Because of the character of the functional feature, it cannot be quaranteed that the performed search is complete. It cannot be excluded that disorders fulfilling the requirements of the functional feature (disorders mediated by the mGluR5 receptor) have not been identified as doing so in the prior art. If such disorders have not been identified in the application either (see the disorders defined in claims 2 and 3), they have not been covered by the search. Consequently, the search has been carried on the basis of the disorders defined in claims 2 and 3 in connection with the compounds defined in the claims .

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/03098

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1,4-15,17 (incomplete)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 02/03098

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